Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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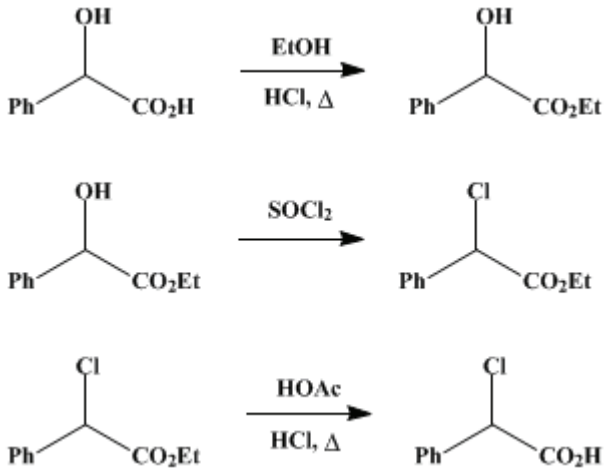
α-CHLOROPHENYLACETIC ACID

[Acetic acid, chlorophenyl-]



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Checked by James Cason, Lois J. durham, and Gerhard J. Fonken.

1. Procedure

A. *Ethyl mandelate*. To 152 g. (1.0 mole) of mandelic acid and 200 ml. of absolute ethanol in a 1-l. round-bottomed flask equipped with a reflux condenser, there is added 100 ml. of absolute ethanol containing about 10 g. of anhydrous hydrogen chloride (Note 1). The solution is heated under reflux on a steam bath for 5 hours, then poured into 1 l. of ice water in a 3-l. beaker (Note 2). A saturated aqueous solution of sodium bicarbonate is added until the mixture is faintly alkaline (Note 3). It is then extracted with two 300-ml. portions of ether in a 2-l. separatory funnel. The ether extracts are washed with a 200-ml. portion of water and dried over 50 g. of anhydrous sodium sulfate. The dried ether solution is concentrated by distillation from a 250-ml. Claisen flask, and the residue is distilled at reduced pressure. There is obtained 147–154 g. (82–86%) of ethyl mandelate, b.p. 144–145°/16 mm. The ester may crystallize upon standing for a prolonged period. It melts at 30.5–31.5°.

B. *Ethyl α-chlorophenylacetate*. Ethyl mandelate (135 g., 0.75 mole) is dissolved in 98 g. (59 ml., 0.82 mole) of thionyl chloride (Note 4) contained in a 500-ml. round-bottomed flask equipped with a reflux condenser capped with a drying tube. The apparatus is allowed to stand in a hood overnight (about 16 hours), at the end of which time the solution is heated under reflux for 30 minutes on a steam bath. The solution is then poured into 750 ml. of ice water contained in a 2-l. separatory funnel (Note 5), and the mixture is extracted with two 300-ml. portions of ether. The combined ether extracts are washed with two 250-ml. portions of saturated aqueous sodium bicarbonate solution and one 250-ml. portion of water. The washed extracts are dried over 45 g. of anhydrous sodium sulfate and concentrated by distillation. The residue is distilled from a 250-ml. Claisen flask at reduced pressure. The yield of ethyl α-chlorophenylacetate is 121–127 g. (81–85%), b.p. 134–136°/15 mm., n_D^{20} 1.5149.

C. α-*Chlorophenylacetic acid*. A solution of 119 g. (0.6 mole) of ethyl α-chlorophenylacetate in 238 ml. of glacial acetic acid and 119 ml. of concentrated hydrochloric acid, contained in a 1-l. round-bottomed flask, is heated under reflux in a hood for 1.5 hours (Note 6). At the end of the heating period the solution is concentrated by heating in an oil bath at 100° at reduced pressure (15–20 mm.) until no further material is distilled (Note 7). The residue is allowed to cool to room temperature and poured slowly, with stirring, into 1-l. of ice-cold saturated sodium bicarbonate solution contained in a 2-l. beaker. Solid sodium bicarbonate is added in small portions until the solution becomes neutral to universal indicator paper (Note 8). The solution is then extracted with two 200-ml. portions of ether in a

2-l. separatory funnel (Note 9), (Note 10). The aqueous phase is placed in a 3-l. beaker and acidified cautiously with ice-cold 12*N* sulfuric acid until the mixture is acid to Congo red paper (Note 11). The oily suspension is extracted with two 200-ml. portions of ether in a 2-l. separatory funnel. The ether extracts are washed with two 100-ml. portions of water and dried over 45 g. of anhydrous sodium sulfate. The dried ether extract is transferred to a 1-l. Erlenmeyer flask and concentrated on a steam bath until ether is no longer distilled. To the residue there is added 500 ml. of warm (50–60°) concentrated hydrochloric acid (in a hood), and the suspension is allowed to cool with occasional swirling (Note 12). Crystallization is completed by chilling in ice, and the product is collected on a sintered-glass funnel. After the product has been dried as much as possible on the funnel it is dried to constant weight in a vacuum desiccator over solid potassium hydroxide. The yield of dry acid is 82–84 g. (80–82%), m.p. 77.5–79.5°. It is satisfactory for most purposes. If very pure material is desired the acid may be recrystallized from three volumes of hexane to give material, m.p. 78.5–79.5°, in 90–95% recovery.

2. Notes

1. The hydrogen chloride may be generated by the method described in *Organic Syntheses*, Coll. Vol. **1**, 293 (1941). It should be dried by passage through concentrated sulfuric acid. The hydrogen chloride may be taken directly from a cylinder, if one is available.
2. The flask should be rinsed with a small portion of water.
3. The amount of bicarbonate solution varies, depending on the weight of hydrogen chloride used. There is usually required 250–350 ml.
4. The submitters used Matheson thionyl chloride without further purification.
5. The flask should be rinsed with a small portion of ether.
6. The solution becomes homogeneous after a few minutes of heating.
7. The checkers found that about 250–270 ml. of distillate is obtained under these conditions.
8. About 90–130 g. of sodium bicarbonate is usually required.
9. When the combined ether layers are dried over sodium sulfate and concentrated, and the residue is distilled at reduced pressure, about 11 g. (10%) of unchanged ethyl α-chlorophenylacetate, b.p. 134–137°/15 mm., is recovered.
10. The solution should be kept ice-cold during the extraction, which must be carried out rapidly lest hydrolysis of the chlorophenylacetic acid to mandelic acid take place.
11. About 70 ml. of acid is required. A 25-ml. excess of 12*N* sulfuric acid is recommended in order to ensure the acidity of the mixture.
12. The objective of the hydrochloric acid treatment is to remove small amounts of mandelic acid from the product. If seed crystals are available, the slurry should be seeded as it is cooled.

3. Discussion

α-Chlorophenylacetic acid has been prepared from mandelonitrile and hydrochloric acid in a sealed tube,[2,3] from mandelic acid and hydrochloric acid in a sealed tube,[4] from α-nitrostyrene and hydrochloric acid in a sealed tube,[5] from phenylglycine, hydrochloric acid, and sodium nitrite,[6] from mandelic acid and phosphorus pentachloride (to give the acid chloride which is then hydrolyzed),[7] and, in poor yield, from mandelic acid and thionyl chloride.[8] In the method described, ethyl mandelate is prepared according to Fischer and Speier.[9] The conversion to the chloroester and the acid hydrolysis step are modifications of a preparation described by McKenzie and Barrow.[8]

References and Notes

1. University of Notre Dame, Notre Dame, Indiana.
2. Spiegel, *Ber.*, **14**, 239 (1881).
3. Meyer, *Ann.*, **220**, 41 (1883).
4. Radziszewski, *Ber.*, **2**, 208 (1869).
5. Priebs, *Ann.*, **225**, 336 (1884).
6. Jochem, *Z. physiol. Chem.*, **31**, 123 (1900).
7. Bischoff and Walden, *Ann.*, **279**, 122 (1894).

8. McKenzie and Barrow, *J. Chem. Soc.*, **99**, 1916 (1911).
9. Fischer and Speier, *Ber.*, **28**, 3252 (1895).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrogen chloride,
hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

phosphorus pentachloride (10026-13-8)

Mandelic acid (90-64-2)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

sodium nitrite (7632-00-0)

potassium hydroxide (1310-58-3)

mandelonitrile (532-28-5)

hexane (110-54-3)

Ethyl mandelate (4358-88-7)

α-Chlorophenylacetic acid,
Acetic acid, chlorophenyl-,
chlorophenylacetic acid (4755-72-0)

Ethyl α-chlorophenylacetate (4773-33-5)

α-nitrostyrene

phenylglycine (103-01-5)